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EXAMINER

ROARK, JESSICA H

ART UNIT

PAPER NUMBER

1644

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Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/772,103

Applicant(s)

CARRENO ET AL.

Examiner

Jessica H. Roark

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 24 February 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-11 and 13-23 is/are pending in the application.
- 4a) Of the above claim(s) 1 (in part) and 16-23 is/are withdrawn from consideration.
- 5) ☒ Claim(s) 14 and 15 is/are allowed.
- 6) ☒ Claim(s) 1-11 and 13 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 16 July 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413) Paper No(s) \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

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### RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 2/24/03 (Paper No. 17), is acknowledged.

Claim 12 has been cancelled.

Claims 1, 7, 14 and 15 have been amended.

Claims 1-11 and 13-23 are pending.

2. Newly submitted claim 1 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: antibody-toxic moiety conjugates comprising an antibody to a B7 costimulatory molecule are structurally distinct from antibody-toxic moiety conjugates comprising an antibody to the CTLA4 protein which is expressed on activated T cells. It is noted that B7 molecules are not normally expressed on activated T cells.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 1 *as it reads on an antibody-toxic moiety conjugates comprising an antibody to a B7 costimulatory molecule* is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 16-23 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction requirement in Paper No. 11.

*Claims 1 (in part), 2-11 and 13-15 are under consideration in the instant application.*

3. This Office Action will be in response to applicant's arguments, filed 2/24/03 (Paper No. 17).

The rejections of record can be found in the previous Office Action (Paper No. 16).

It is noted that New Grounds of Rejection are set forth herein.

### *Specification*

4. The disclosure stands objected to because of the following informalities: "Blanks" are present in the specification on pages 4, 5 and 28 for ATCC and hybridoma designations of the CTLA4 antibodies.

Applicant's request to hold correction in abeyance until such time as the ATCC designations can be provided is acknowledged.

Appropriate correction is required but held in abeyance.

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### ***Claim Objections***

5. Claims 2-11 and 13 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim.

The specification on page 7 at line 23-32 (as amended 2/24/03) defines a "costimulatory receptor" to include receptors which transmit a costimulatory signal to an immune cell (e.g., CD28) and distinguishes a "costimulatory receptor" from an "inhibitory receptor", which includes receptors which transmit a negative signal to an immune cell (e.g., CTLA4).

In view of the definitions provided in the specification as filed, a claim which limits the antibody to one which is specifically reactive with CTLA4 (i.e., claim 2 and claims which depend therefrom), do not further limit claim 1, which recites a genus of antibodies to a "costimulatory receptor".

Applicant is required to place the claims in proper dependent form either by rewriting claim 2 in independent form, or by amending claim 1 to provide a recitation of a genus which encompasses CTLA4 in view of the definitions set forth in the specification as filed.

### ***Claim Rejections - 35 USC § 112 second paragraph***

6. The following is a quotation of the second paragraph of 35 U.S.C. 112.

*The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.*

7. Applicant's amendment, filed 2/24/03, has obviated the previous rejection of claims 7 and 12 under 35 U.S.C. 112, second paragraph.

8. Claims 1 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 1 is ambiguous because it is unclear what the metes and bounds of the antibody specificity is. In particular, although as noted supra the specification on page 7 at lines 23-32 (as amended 2/24/03) provides a definition of a "costimulatory receptor", the construction of the dependent claim creates an ambiguity as to the types of molecules which are "costimulatory receptors" as recited in instant claim 1. The specification appears to be consistent throughout in its identification of CTLA4 as an "inhibitory receptor" and not a "costimulatory receptor".

It is suggested that Applicant amend claim 1 to substitute CTLA4 for the current recitation of "costimulatory receptor".

B) Claim 7 recites in the last line "compared to an antibody without the substitution of amino acid 83". There is insufficient antecedent basis for this limitation in the claim because the substitution of amino acid 83 in claim 7 is stated to be in the context of the CTLA4 sequence shown in SEQ ID NO:2, not in the amino acid sequence of the antibody.

It is suggested that Applicant amend the claim to clearly set forth that the comparison is between binding of an antibody to CTLA4 having a substitution at amino acids 83 or CTLA4 without the substitution at position 83. For examination purposes, the claim will be so interpreted.

C) Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

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***Claim Rejections - 35 USC § 112 first paragraph***

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

*The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

10. Claim 7 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The following *written description* rejection is set forth herein. *This is a New Matter rejection for the following reasons:*

Applicant's amendment asserts that no New Matter has been added and points to the specification at page 78, line 19 to page 79 at line 13, page 5 at lines 22-25 and to Figure 2B for support for the newly added limitation "results in reduced binding of the antibody by at least about 80% compared to an antibody without the substitution of amino acid 83".

As noted supra this limitation has been interpreted to compare antibody binding to CTLA4 with and CTLA4 without the position 83 substitution. However, the specification still does not appear to provide an adequate written description of the instant limitation.

Applicant points out that Figure 2B shows ELISA results indicating that binding of antibody 26 to the E46 CTLA4 mutant (which using the numbering set forth in SEQ ID NO:2 corresponds to a substitution in amino acid 83) is reduced by about 80% compared to binding of antibody 26 to wildtype CTLA4.

The Examiner acknowledges that data in Figure 2. However, the data are for a single species of antibody, antibody 26. Instant claim 7 is drawn to a genus of antibodies having the same binding properties as a single species of CTLA4 antibody. While the disclosure sets forth the genus of antibodies to CTLA4 and provides 1 species with the instantly recited properties; the Examiner was unable to identify adequate written support in the specification for the now claimed subgenus of CTLA4 antibodies.

Disclosure of a genus and species of subgenus within that genus is not sufficient description of subgenus to satisfy description requirement of 35 U.S.C. 112, unless there are specific facts which lead to determination that subgenus is implicitly described. Ex parte Westphal, 26 USPQ2d (BPAI 1993). In re Smith 173 USPQ 679 (CCPA 1972).

The instant claims now appear to recite limitations which were not clearly disclosed in the specification and claims as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in the present claims, which did not appear in the specification or original claims, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

*Applicant is required to cancel the New Matter in the response to this Office Action.*

Alternatively, Applicant is invited to clearly point out the written support for the instant limitations.

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11. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The following *written description* rejection is set forth herein.

Applicant's arguments and amendment to claim, each filed 2/24/03, have been fully considered. Applicant's argument that claim 1 as amended complies with the written description requirement has not been found convincing for the following reasons:

Claim 1 as amended recites that the antibody specifically recognizes "a costimulatory receptor expressed on an activated T cell" as part of the invention.

The Examiner acknowledges Applicant's comments that the specification describes on page 2 at lines 19-20 the costimulatory receptor ICOS, which is also expressed on activated T cells.

Claim 1 as currently amended has added the requirement that the molecule expressed on the activated T cell be a "costimulatory molecule". Functional criteria for a "costimulatory molecule" are provided in the specification on page 7 at line 23 to page 9 at line 5 and on page 1 at lines 9-26.

CD28 and ICOS appear to be the only molecules disclosed in the specification which meet the functionally defined criteria of a "costimulatory receptor" (as distinct from an "inhibitory receptor" such as CTLA4). Of CD28 and ICOS, only ICOS is expressed on activated T cells but is not expressed on naive T cells; although it is acknowledged that the broadest reasonable interpretation of instant claim 1 is that so long as the molecule is also expressed on an activated T cell (which CD28 is), then there is currently no requirement that the molecule ONLY be expressed on activated T cells.

However, the specification still does not appear to provide a disclosure of any particular structure that conveys an expression pattern that includes activated T cells. Neither does the instant recitation requires any structural limitation with respect to the "costimulatory receptor". The instant recitation is essentially claiming in terms of function and cell type expression of the recited genus of molecules; therefore, there is substantial variation permitted within a genus for which Applicant has disclosed only two members.

A definition by function alone "does not suffice" to sufficiently describe a coding sequence "because it is only an indication of what the gene does, rather than what it is." Eli Lilly, 119 F.3 at 1568, 43 USPQ2d at 1406. See also Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing Amgen Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991)). Although the instant claims are drawn to proteins rather than DNA, the instant recitation of a "costimulatory receptor" still only provides a description of what the protein does, rather than what it is.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is invited to point to clear support or specific examples of the claimed invention in the specification as-filed.

The rejection is therefore maintained as applied to the amended claim.

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12. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody-toxic moiety conjugate comprising an antibody that specifically recognizes the costimulatory receptors CD28 and ICOS, certain other art-recognized molecules which can provide a non-TCR mediated signal to stimulate T cells, such as ACT-4/OX-40R, as well as the inhibitory receptor CTLA4; does not reasonably provide enablement for an antibody-toxic moiety conjugate comprising an antibody that specifically recognizes *any* "costimulatory receptor" expressed on an activated T cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Applicant's arguments and amendment to claim, each filed 2/24/03, have been fully considered. Applicant's argument that claim 1 as amended is enabled has not been found convincing for the following reasons:

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized in In re Wands (8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and amount of experimentation required to enable one of skill in the art to practice the claimed invention.

There is insufficient guidance in the specification and a limited number of working examples such that one skilled in the art could practice the invention as broadly claimed. The specification discloses the costimulatory receptors CD28 and ICOS. The specification also discloses the inhibitory receptor CTLA4. However, the scope of the instant claim encompasses antibody-toxic moiety conjugates in which the antibody is specific for any molecule that is a "costimulatory receptor" and expressed on activated T cells. A "costimulatory receptor", as defined in the specification on page 7 at line 23 to page 9 at line 5 and on page 1 at lines 9-26 is a molecule which transmits a costimulatory signal to a cell, which is a non-activating receptor (i.e., TcR) signal that induces proliferation or effector function. A molecule with any structure is thus a costimulatory receptor so long as it has the requisite function.

However, "[i]t is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992).

The identity of other molecules which meet this claim limitation is highly unpredictable. Neither does the specification appear to provide sufficient guidance as to how to identify other costimulatory receptors.

Applicant's argument that methods were known in the art for identifying other activation markers is acknowledged. However, the instant claim is drawn to costimulatory receptors. It would require undue experimentation of the skilled artisan to identify other molecules meeting this claim limitation, prepare antibodies to the molecules, and then provide an antibody-toxic moiety conjugates comprising the antibodies.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In view of the insufficient guidance in the specification and limited number of working examples; the experimentation left to those skilled in the art to make the instantly recited antibody-toxic moiety conjugates as broadly recited, is unnecessarily, and improperly, extensive and undue.

The rejection is therefore maintained as applied to the amended claim.

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13. The previous rejection of claims 14 and 15 under 35 U.S.C. 112, first paragraph, enablement in withdrawn in view of Applicant's amendment, filed 2/24/03 and Applicant's arguments with respect to the teachings of Kuchroo et al. (U.S. Pat. No. 6,207,156, of record), also filed 2/24/03.

14. Applicant's cancellation of claim 12 in the amendment filed 2/24/03 has obviated any issues under 35 U.S.C. 112, first paragraph, deposit.

***Claim Rejections – 35 U.S.C. §§ 102 and 103***

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

*(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.*

16. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Godfrey et al. (U.S. Pat. No. 5,821,332, issued 10/13/1998, see entire document, of record), as evidenced by Swiss-Pat #P43489 (TNR4\_HUMAN, Release 42, September 2003) and Godfrey et al. (J. Exp. Med. 1994; 180:757-762).

Applicant's arguments and amendment to claim, each filed 2/24/03, have been fully considered but have not been found convincing.

Applicant's argues that claim 1 as amended is not anticipated by Godfrey et al. because ACT3 is not a "costimulatory receptor" as recited in the amended claim.

Godfrey et al. '332 teach that the ACT-4 polypeptide has the amino acid sequence set forth in SEQ ID NO:2 (see e.g., column 4, Figure 5 description, and SEQ ID NO:2). Godfrey et al. state that the expression of ACT-4 on the surface of activated CD4 T cells suggests that ACT-4 has a role in activating these cells (column 10, especially lines 18-33).

P43489 provides evidence that ACT-4 of Godfrey et al. '332 is, among other names, also known as the human OX40L receptor (compare amino acid sequence of SEQ ID NO:2 of Godfrey et al. '332 and that set forth in P43489).

Godfrey et al. 1994 characterize the ligand of OX40 and show that OX40 on the surface of CD4 T cells acts as a costimulatory receptor (see entire document, e.g., Abstract).

As previously noted, Godfrey et al. '332 teach the human polypeptide ACT-4 and that this receptor is expressed only on the surface of activated CD4 T cells, its expression being absent on resting T cells as well as on other cell types in physiological conditions (see entire document, but especially columns 9-10 and in particular column 10 at lines 11-17).

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Godfrey et al. '332 also teach antibodies to the human ACT-4 protein, including monoclonal antibodies (see especially columns 14-18).

Godfrey et al. '332 teach that the anti-ACT-4 antibodies can be conjugated to a toxic moiety for use as an immunotoxin (see especially the bridging paragraph of column 17-18). Godfrey et al. teach that there are many suitable toxin components (column 18 at lines 6-11), including the bacterial toxin ricin (column 18 at lines 6-11 in view of column 10 at lines 47-49).

Thus in contrast to Applicant's assertions in the response filed 2/24/03, ACT4 is a costimulatory receptor expressed on an activated T cell.

The reference teachings thus anticipate the instant claimed invention.

The rejection is maintained as applied to the amended claim.

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

*(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 1-7, 10-11 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Godfrey et al. (U.S. Pat. No. 5,821,332, of record) and Kuchroo et al. (U.S. Pat. No. 6,207,156, of record).

Applicant's arguments, filed 2/24/03, have been fully considered but have not been found convincing.

Applicant argues that there is not motivation to combine the teachings of Godfrey et al. with that of Kuchroo et al. because Godfrey et al. teach antibody-toxin conjugates for the purpose of eliminating cells and suppressing an undesired immune response, while Kuchroo et al. teach that anti-CTLA4 antibodies are useful as immune response enhancers.

The claims are drawn to an antibody-toxic moiety conjugate comprising a humanized monoclonal antibody that specifically recognizes human CTLA4, including wherein the antibody blocks binding of CTLA4 to CD80 or CD86.

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As previously noted, Godfrey et al. teach the human polypeptide ACT-4 and that this receptor is expressed only on the surface of activated CD4 T cells, its expression being absent on resting T cells as well as on other cell types in physiological conditions (see entire document, but especially columns 9-10 and in particular column 10 at lines 11-17).

Godfrey et al. also teach antibodies to the human ACT-4 protein, including monoclonal antibodies and humanized monoclonal antibodies (see especially columns 14-18).

Godfrey et al. teach that the anti-ACT-4 antibodies can be conjugated to a toxic moiety for use as an immunotoxin (see especially the bridging paragraph of column 17-18). Godfrey et al. teach that there are many suitable toxin components (column 18 at lines 6-11), including the bacterial toxin ricin (column 18 at lines 6-11 in view of column 10 at lines 47-49).

Godfrey et al. teach that immunotoxins comprising anti-ACT-4 antibodies, including humanized anti-ACT-4 antibodies, can be used as therapeutic reagents to suppress undesired immune responses by selectively eliminating activated CD4 T cells (see entire document, but especially column 22 at lines 11-36).

Godfrey et al. teach that therapeutic agents which selectively eliminate activated cells are particularly advantageous because such reagents eliminate the cells involved in the undesired immune response while sparing non-activated T cells and preserving a residual immune capacity (see comments at column 22 lines 27-36).

Godfrey et al. review in column 2 the art-recognized motivation for developing multiple reagents which targeted different cell-surface receptors for use in methods of suppressing undesired immune responses. In particular, Godfrey et al. note that when using a single therapeutic agent to suppress an undesired immune response in a patient the patient may develop an immune response to the agent which prevents its effect and that cells expressing the target antigen may adapt to the therapy by ceasing to express the target antigen.

Finally, Godfrey et al. also note that the art recognized that while it was desirable to develop multiple reagents, the ideal reagents block only undesired immune responses while leaving a residual capacity to effect desirable immune responses (see especially comments at column 2, lines 7-40).

Kuchroo et al. teach monoclonal antibodies to human CTLA4 which bind to CTLA4 and prevent the interaction of B7 with human CTLA4 (see entire document, e.g., "Summary of the Invention" at columns 2-4). Kuchroo et al. teach that the anti-human CTLA4 monoclonal antibodies may be humanized (e.g., column 2 at lines 48-60 and columns 7-9). Kuchroo et al. review that CTLA4 is a molecule expressed only on activated T cells (see comment at column 1, lines 60-67). Kuchroo et al. further review that "B7" includes B7-1 and B7-2 (e.g., column 1 at lines 27-50). B7-1 is an alternate name for CD80 and B7-2 is an alternate name for CD86.

Kuchroo et al. do not teach an antibody-toxic moiety conjugate comprising a humanized monoclonal antibody that specifically recognizes human CTLA4, including wherein the antibody blocks binding of CTLA4 to CD80 or CD86.

The Examiner has previously argued that given the teachings of Godfrey et al. that it was desirable to produce toxins conjugated to different antibodies which each targeted different cell surface molecules expressed selectively on cells involved in undesired immune responses in order to eliminate the cells in vivo and the teachings of Kuchroo et al. of antibodies to the CTLA4 antigen expressed on activated T cells; it would have been obvious to the ordinary artisan at the time the invention was made to produce antibody-toxin moiety conjugates comprising the anti-CTLA4 antibodies of Kuchroo et al.

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Specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See CTS Corp. v. Electro Materials Corp. of America 202 USPQ 22 (DC SNY ); and In re Burckel 201 USPQ 67 (CCPA).

That Kuchroo et al. teach the enhancement of an immune response using anti-CTLA4 antibodies not conjugated to a toxic moiety does not alter the fact that Kuchroo et al. also teach that CTLA4 is molecule expressed only on activated T cells. Viewed in the context of the teachings of Godfrey et al., the ordinary artisan would have appreciated that even though in certain instances antibodies to CTLA4 may be used to enhance an immune response, CTLA4 could also serve as a target for the elimination of T cells when the T cells were participating in an undesired immune response.

As noted supra, Godfrey et al. teach that many different toxins are suitable for conjugating to antibodies, and points in particular to the bacterial product ricin (column 18 at lines 6-11). As also noted supra, the antibodies of Kuchroo et al. prevent the interaction of B7 with human CTLA4 (see entire document, e.g., "Summary of the Invention" at columns 2-4). In addition, the antibodies of Kuchroo, because they do prevent the interaction of B7 with human CTLA4 would also necessarily bind to a region of the CTLA4 molecule in spatial proximity to the site of CTLA4 binding to a costimulatory molecule. Similarly, binding of the antibodies of Kuchroo et al. would necessarily be modulated by a substitution in CTLA4 at position 83 of SEQ ID NO:2.

Applicant has argued that there was no reasonable expectation of success in combining the teachings of Godfrey et al. and Kuchroo et al. because ACT4 is a member of a different family of molecules than CTLA4 and ACT4 is "unique" among activation antigens.

The Examiner has previously noted that the ordinary artisan would have had a reasonable expectation of producing the instant antibody-toxic moiety conjugate given the availability of the anti-CTLA4 antibodies of Kuchroo et al. and the standardized techniques for conjugating any of a variety of toxic moieties to an antibody.

It is further noted that the instant claims are drawn to a product. The motivation of the ordinary artisan to produce the instantly claimed product would also not have been inhibited by the fact that CTLA4 and ACT4 belong to different receptor families or the "uniqueness" of ACT4. Antibody linked toxins to a variety of receptor families were well known in the art at the time the invention was made for depletion of various cell types. The identification of cell surface molecules expressed predominantly on activated T cells provided the ordinary artisan with an opportunity to selectively eliminate activated T cells, but spare T cells not involved in the undesired immune response. As noted supra, Godfrey et al. clearly teach the desirability of selective targeting, and the desirability of targeting more than one receptor.

The amendments to the instant claims do not appear to alter the rejection of record. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The rejection is maintained as applied to the amended claims.

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19. Claims 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Godfrey et al. (U.S. Pat. No. 5,821,332, of record) and Kuchroo et al. (U.S. Pat. No. 6,207,156, of record) as applied to claims 1-7, 10-11 and 13 above, and further in view of Hamann et al. (U.S. Pat. No. 5,773,001, of record).

Applicant's arguments, filed 2/24/03, have been fully considered but have not been found convincing.

Applicant argues that the teachings of Hamann et al. do not compensate for the deficiencies of Godfrey et al. and Kuchroo et al.

Applicant's arguments with respect to Godfrey et al. and Kuchroo et al. have been addressed supra.

As previously noted, Godfrey et al. teach that any of a number of toxins are suitable components of an antibody-toxic moiety conjugate (column 18 at lines 6-11).

Hamann et al. teach that calicheamicin is a potent toxin that can be conjugated to antibodies, including humanized antibodies, and used to eliminate cells expressing the antigen recognized by the antibody of the conjugate (see entire document, especially "Background of the Invention" at columns 6-20).

he Examiner maintains that it would therefore have been obvious to the ordinary artisan at the time the invention was made to substitute the carbohydrate calicheamicin for the toxin moiety of the antibody-toxin immunoconjugate taught by Godfrey et al. and Kuchroo et al. The ordinary artisan would have been motivated to make such a substitution in view of the recognized suitability of calicheamicin in antibody-toxin conjugates, and because Hamann et al. teach that calicheamicin is a potent toxin. Given the teaching of antibody-calicheamicin conjugates by Hamann et al., the ordinary artisan would have had a reasonable expectation that the antibodies of Kuchroo et al. could also be conjugated to calicheamicin to produce antibody-toxic moiety conjugate comprising an antibody that specifically recognizes CTLA4 and a toxic moiety that is the carbohydrate calicheamicin. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The rejection is therefore maintained.

Art Unit: 1644

*Conclusion*

20. Claims 14 and 15 appear to be allowable.

21. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

22. This application contains claims 16-23 drawn to an invention nonelected with traverse in Paper No. 11. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.  
Patent Examiner  
Technology Center 1600  
June 2, 2003

*Phillip Gambel*  
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